



TSD Activities Update (July to Sept'2023)

**MSN Life Sciences Pvt. Limited,
Unit-III**

- Capacity Enhancement or Release
- Reduction / Recovery & recycling the Solvent
- Continuous improvements on commercial Products
- Reduction in Effluent
- Trouble shooting & Customer Support for PSD & XRD.
- Implementation of New Technology
- Implementation of New Products in coordination with R&D
- Implementation of KSM & CIP's in coordination with Plant R&D
- New Production Blocks/ Projects Related Activities

Capacity Enhancement or Release

Product: Ranolazine

RLNA1: Scale-up from 500 Kg in A-Block to 900 Kg in C-Block,

RLNB1: Scale-up from 500 Kg in A-Block to 800 Kg in C-Block.

RLNZ1: Scale-up from 700 Kg in B/A-Block to 1100 Kg in C-Block.

RLNZ2: Scale-up from 400 Kg in E/F-Block to 1000 Kg in C-Block.

RLNZ3: Additional cleanroom E-III along with existing F-IV with 525 Kg Batch Size.

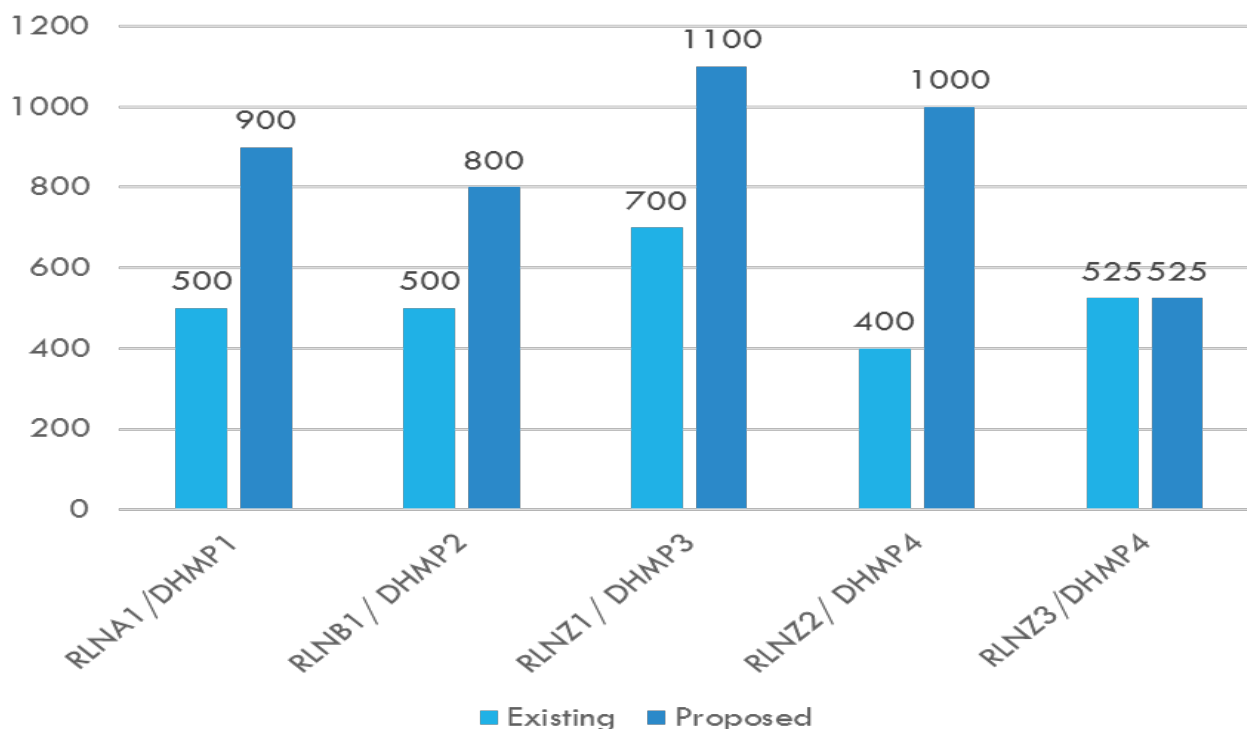
Existing: 5.5 TPM.

Proposed: 17 TPM.

Current Status: RLNA1 Scale-up completed, Remaining stages scale-up to be started after receiving raw materials.

Total Release of ~8823 KL Days (~14%)

RLNA1/DHMP1		RLNB1/DHMP2		RLNZ1/DHMP3		RLNZ2/DHMP4 (Crude)		RLNZ3/DHMP4 (Pure)	
Existing	Proposed	Existing	Proposed	Existing	Proposed	Existing	Proposed	Existing	Proposed
500 Kg	900 Kg	500 Kg	800 Kg	700 Kg	1100 Kg	400 Kg	1000 Kg	525 Kg	525 Kg



Capacity Enhancement or Release

Product:

Flecainide Acetate

FNDA1: Scale-up from 130 Kg to 325 Kg in existing B-Block,

FNDA2: Scale-up from 145 Kg in F-Block Phase-IV to 450 Kg in E-Block Phase-III/IV.

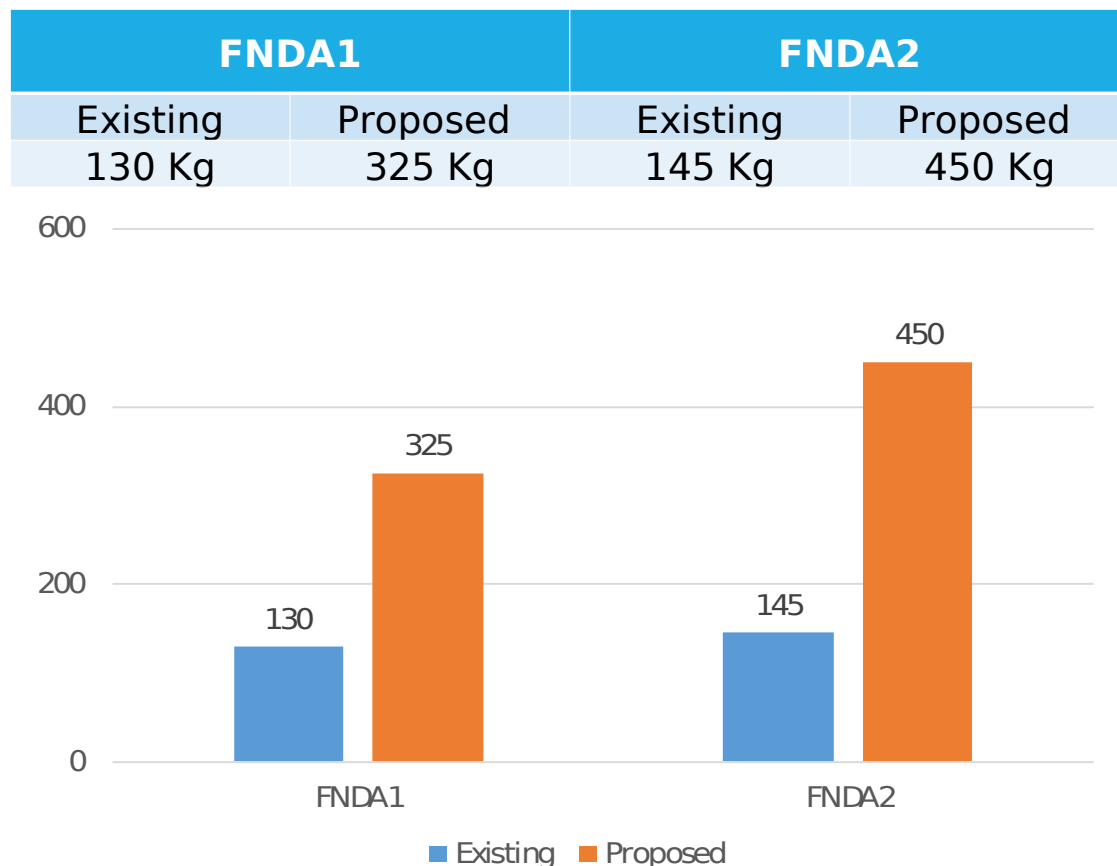
Existing: 0.91 TPM.

Proposed: 3.22 TPM.

Current Status: Scale-up proposed to meet the market demand from various customers.

Note: Tentatively scale-up will be initiated in next financial year as per marketing requirement.

Total Release of ~995 KL Days (~50%)



Trouble shooting

PIN MILL Trials for Levetiracetam To Meet Desired PSD

Product & Stage:

Levetiracetam Pharma (LVTC2)

Existing Situation

Levetiracetam Pharma material is coarser and PSD is not meeting the requirement. ~5 to 6 times Milling operation is being performed in Multimill for Sieve Top materials to meet the required PSD.

Requirement

Required PSD range & Regular Trend in validations is D90 ~165 Microns.

Proposal:

- 1) As the required PSD (~165 microns) is less than the multi mill mesh size (i.e. 0.25 mm/ 250 microns), material is constantly passing through miller mesh and PSD is not meeting the requirement.
- 2) Pin Mill Trials were performed for Levetiracetam Sieve Top material to meet the desired PSD (D90 ~165 microns) and to avoid multiple milling operation (~5-7 times)

Results & Way forward:

Below are the Pin Mill trail results.

With 3000 RPM, D10-20.3 microns, D50-81.2 microns & D90-187 microns

With 3300 RPM, D10-17.6 microns, D50-70.5 microns & D90-164 microns.

Pin mill material with 3300 RPM is meeting the requirement, to be implemented in regular commercial batch.

Material loss can be avoided, Effective clean room utilization & manpower by implementing Pin Mill operation in place of multiple milling operations (5-7 times).

New Products at LS-III

SITAGLIPTIN (Enzyme Route)

Stage code	Batch Number	T&V	Batch size (Kg)	Output (Kg)	Yield (w/w)	Yield range	Remarks
SATM1	SATM100123	T1	100	122.43	1.22	1.05-1.29 w/w	
	SATM100223	T2	450	601.16	1.34	1.20 w/w to 1.36 w/w	
	SATM100323	V1		595.73	1.32		
	SATM100423	V2		591.28	1.31		
	SATM100523	V3		598.32	1.33		
SATM2	SATM200123	T1	122	144.2	1.18	1.19 to 1.45 w/w	
	SATM200223	T2	550	649.1	1.18	1.06 to 1.29 w/w	
	SATM200323	V1		666.48	1.21		
	SATM200423	V2		693.4	1.26		
	SATM200523	V3	700	915.7	1.31		
SATM3	SATM300123	T1	143	93.74	0.66	0.74 to 0.91 w/w.	
	SATM300223	T2	450	313.6	0.70	0.61 to 0.75 w/w	
	SATM300323	V1	450	318.81	0.71		
	SATM300423	V2	415	286.87	0.69		
	SATM300523	V3	415	278.2	0.67		
SATM4 (Mono Hydrate)	SATM400123	T&V	375	Tech Transfer Completed, Trial Batch to be started			Experimental Batch with 125 Kg B.Size completed
	SATM400223	V1					
	SATM400323	V2					
	SATM400423	V3					
SATD12M (Anhydrous)	T&V		275	Tech Transfer Completed, Trial Batch to be started			
SATD14M (HCl)	T&V		400	Tech Transfer Pending			

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New Products at LS-III

Upcoming New Products Status

S.#	Product	No of Stages	Status			
			Raw Materials	Tech Transfer	Execution	Remarks
1	Vonoprazan Fumarate	5	Raw materials Received, Use-test u/process in LS3 R&D.	Stage-1 (VPRN2B) TT Completed	To be started after receiving KSM & Method Transfer activity.	
2	Mesalamine	3	All Raw materials Received	Completed	To be started after completion of Raw Materials Method Transfer activity, Analysis.	
3	Atogepant	4	Key Raw materials Not yet received. Common Raw materials indent pending	Pending	NA	ATGB3 stage Experimental batch executed with 16 Kg B.Size in F-Block.
4	Medetomidine	4	To be Indented	Pending	NA	

Implementation of KSM & CIP's in coordination with Plant R&D

Implementation of CIP's in coordination with Plant R&D

S. #	Product	Stage	B.Size	Location	Major Changes	Status	Remarks
1	Vildagliptin	VGTB1 (Stage-1)	160	F-Block	1) Amidation reaction at 1.0-1.5 Kg/cm² pressure to reduce cycle time & Ammonia gas consumption from 9 cylinders to 5 cylinders. 2) Solvents: DMF Solvent reduced from 4.5 Vol to 2 Vol, Toluene reduced from 8 vol to 1 Vol. 3) Chloroacetyl chloride reduced from 1.48 times to 1.2 times, Cyanuric chloride Qty reduced from 0.8 times to 0.64 times. 4) Process cycle time reduced from 11 Days to 7 Days.	1) To avoid delay of Unwanted filtration in existing PNF, proposed to perform filtration in centrifuge. In 100 kg scale for two batches, filtration completed in ~3 hrs 30 min (including feeding, washing & Spinning). 2) For 100 Kg. Batch 0.886% w/w & 0.86% w/w yield observed in two consecutive batches 3) ~128 Kg (~0.8 w/w yield) obtained for 160 Kg scale-up batch. 4) As per discussion with subba Rao sir, Unwanted filtration followed by quenching, extraction & M-470 pH to be completed in 2-2.5 Hrs to avoid degradation (Quenching, MDC Extraction 3 times followed by M-470 pH Adjustment).	
2	Rosuvastatin Calcium	RVST1/RSC2B	150	E-Block	Methanol solvent in place of IPA & single purification in place of two purifications.	Experimental batch with 150 Kg B.Size Completed, Output - 134.31 Kg (0.89% w/w) compared to 0.78-0.8 w/w in existing process. Scale-up batch with 350 Kg B.Size to be planned in B-Block.	8

Projects Related Activities at LS-III

S.#	Block	Activity	Status	Remarks
1	G-Block	Utility capacities (CT Water, Chilled water, Brine, etc.)	Utility load calculated and proposed capacities submitted to ESD Dpt.	
2	F-Block	Small Scale Clean room facility (1.0 Kg output) for Extraneous matter/ Foreign particles Free API Samples to various customers (Japan)	Equipment list to be finalized for Cost estimation.	
3	SRS Area	Proposal for Continuous Distillation column.	Concept notes discussed on 08/09/2023. P&ID, Floor wise equipment layout completed, budget to be estimated. To be implemented for one column & one Reactor in existing at LS-III.	
4	H,I,L,K & J-Blocks Tank Pad	Phase-1 Tanks list finalised for I-Block	Plant sign-off completed, further approval pending	
5	G-Block	Filtration & Drying equipment finalization for Capacity enhancement of Pregabalin, Clopidogrel Bisulfaate, Rosuvastatin Calcium & Atorvastatin Calcium in G-Block.	Discussion completed with Subba Rao sir and Drier capacities finalised as per specific product requirement. Phase-1: Pregabalin (5 KL ANFD followed by 4 KL RCVD) Phase-2: Rosuvastatin Calcium (60" x 2 Nos Followed by 2.5/3.0 KL RCVD- 2 Nos) Phase-3: Clopidogrel Bisulfate (60" x 2 Nos Followed by 3 KL RCVD, 96 Trays VTDR- 1 No. for other products) Phase-4: Atorvastatin Calcium (60" x 2 Nos Followed by 1.23 Trays VTDR- 1 No.)	

Other TSD Activities at LS-III

Other TSD Activities at LS-III

S.#	Catogery	Activity	Status	Remar ks
1	Effluent Reduction Project	Optimised process received from R&D to reduce effluent & Solvent quantities. CGBS1: 1) Total 9.8 vol of Potable water reduced in process. 2) MDC replaced with Toluene & Aq NH3 replaced with NH3 Gas. CGBS2: 1) Total 8 vol of purified water reduced in process. 2) Paraformaldehyde quantity reduced from 2.6 times to 1.5 Times.	Use test completed in Lab. Batch size & Facility to be finalised for equipment mapping & process lines modification.	
2	New Technology	Multi Candle Filter (6 m2 Area) & Press Filter (15 m2 Area) for I-Block	Procurement to be initiated, Quotation to be received from SCM. PR pending, to be raised after receiving Quote.	
3	Trouble shooting	M-964 Purification taken due to colour & low Assay issue. Two purification batches completed with yields 0.81 w/w & 0.82 w/w for 400 kg B.Size.	1) M-964 Assay increased to 99% from ~73-78% after purification. 2) Yield increased from 1.24 w/w to 1.31 w/w with purified M-964 in SATM2 stage of Sitagliptin.	10
4	Capacity Enhanceme	Sitagliptin Phospate Mohohydrate (Synthetic Route) Document Scale-	Batch Size increased from 125 Kg to 525 Kg input based on available 96 Trays Drier at E-Block Phase-III.	

Customer Support for PSD & XRD

S.#	Block	Product	Activity	Status	Remarks
1	F-Block	Opicapone	2.0 Kg x 2 Nos Samples for ABBOTT with Below PSD Specifications. <u>Fine Material (2 Kg):</u> D(95): Not more than 10 μm D(50): Not more than 6 μm D(10): Not more than 4 μm <u>Coarser Material (2 Kg):</u> D(95): Not more than 70 μm D(50): Between 10-45 μm D(10): Not less than 4 μm	Existing Material PSD Trend is D(95) ECD: 11-14 μm D(50) ECD: 4-5 μm D(10) ECD: 2-3 μm Sifting (or) Micronization Trials to be taken for Fine material requirement. Experiments u/process in PD Lab for coarser material requirement.	

Thank You